REMARKS

In an Office Action mailed June 19, 2002, the Examiner withdrew a requirement for restriction, withdrew rejections of Claims 1-9 under 35 U.S.C. §112, first paragraph, withdrew rejections under 35 U.S.C. §102(a) and 35 U.S.C. §103, but rejected Claims 1-42 under 35 U.S.C. §112, second paragraph for alleged indefiniteness. The Examiner acknowledged that the claims are free of the prior art of record and made of record certain additional art not relied upon, but considered pertinent to the applicants' disclosure. Each remaining issue will be addressed separately below. In view of the amendments note above and the arguments presented herein, applicants respectfully request reconsideration of the merits of this patent application.

Rejections Under 35 U.S.C. §112, second paragraph:

Claims 1, 2, 26, 30, 31 and 39 are rejected as unclear and confusing in the recitation of crossing "gametes." Applicants believe that the specification makes quite clear to the skilled artisan at page 12, lines 19-25 and elsewhere, that while animals can be crossed in the methods of the invention, it is more broadly appropriate to speak of crossing gametes since it is the contribution of the gametes that yields the genetic ramifications in the method. The distinction is noted because of the ability pointed out in the specification to employ harvested male gametes in crosses in a manner familiar to the skilled artisan. Accordingly, the reference in the claim to crossing of gametes, while perhaps colloquial, clearly teaches the skilled artisan that the crosses of the invention can be performed using *in vitro* fertilization methods or by traditional breeding methods. No amendment is believed necessary.

Claims 1, 26 and 30 are said to be vague and unclear for the recitation of "the F_1 progeny that carry the dominant allele also carry at least one random mutation." Claims 1, 26 and 30 now recite a method for identifying particular F_1 individuals, where identification in the method step indicates that at least one F_1 individual possesses an index phenotype-modifying mutation. In the case of Claim 26, the mutation modifies an allele at a genetic locus that modifies tumor multiplicity.

Claims 3 and 32 are said to be vague and indefinite in the recitation of "extreme outlying phenotype." Applicants maintain, as set forth in the specification on page 13, lines 4-10, that the skilled artisan understands that the term extreme can only be specified on a case-by-case basis. The applicants there note that in some cases a level below the tenth percentile or above the ninetieth percentile could be extreme, whereas in another case, extreme levels might be established at the second and 98^{th} percentiles, respectively. The full

paragraph bridging pages 12 and 13 sets forth the strengths and shortcomings of screens that evidence an extreme enhancer or suppressor phenotype. The Examiner is invited to solicit further clarification as needed. However, applicants maintain that the term is well understood by the skilled artisan.

Claim 4 is said to be unclear for its recitation of a segregating mutation that "is a heterozygous modifier," because, in the view of the Examiner, "it is unclear how a single mutation can at the same time both enhance and suppress an observed phenotype/activity." Applicants respectfully suggest that the Examiner has misread the claim. Claim 4 clearly does not require both enhancement and suppression, but rather allows that the heterozygous modifier can be selected from a group consisting of an enhancing modifier and a suppressing modifier. Accordingly, the claim merely indicates that the modifier can either enhance or else suppress. Again, the Examiner is invited to seek further clarification as needed, or to suggest alternative language to convey this concept. However, applicants understand the Markush group to be an appropriate vehicle for doing so.

Claims 6 and 35 are said to be unclear and confusing for recitation of "share an isogenic background," because, in the Examiner's view, both the strains are clearly genetically different. As is clear from the specification and the claims, the so-called "index inbred strain" carries a congenic dominant allele at a locus known to confer an index phenotype. The "founder inbred strain" carries random point mutations relative to a wild-type animal of the founder inbred strain. The recitation of a shared isogenic genetic background in Claims 6 and 35 means that apart from the congenic dominant allele on the one hand and the random point mutations on the other, the founder and index inbred strains of Claims 6 and 35 share a genetic background. One strength of the so-called isogenic modifier screening method (see page 13, line 34 et seq.) is the elimination of interstrain genetic differences, apart from those differences as stated in the claims, thereby facilitating identification of a segregating single mutagen-induced modifier, as described. One preferred mapping method mapping further employs a mapping partner strain that likewise shares the genetic background of the founder and index strains. The Examiner states that the metes and bounds of the claim are unclear even if some of the genetic background was similar. However, when the same inbred strain is employed to produce the index inbred strain and the founder inbred strain, the claim is satisfied. If the index and founder inbred strains derive from different inbred strains, the method will fall within other embodiments of the invention, but the specific power of the isogenic embodiments will be lost. The power of the method is particularly evident when the mapping partner strain is used in conjunction with the isogenic

screening method. This principal derives not from issues arising under the patent law, but rather from the technical desire to minimize the differences between the founder and index inbred strains in these embodiments of the invention. The relevant claims relating to isogenic screening and mapping as amended refer consistently to the founder background, although reference could just as easily be made to the index strain, as it shares the same background.

Applicants also note that Claims 23 and 25 are amended to remove inaccurate references to an "founder isogenic strain."

Claim 7 is said to be incomplete because it is directed to "mapping a segregation mutation." In the Examiner's view, the steps of the method only result in sib-mating of progeny. Again, applicants respectfully suggest that the Examiner misreads Claim 7. The step added in Claim 7 is the step of mapping the segregating mutation using a mapping partner strain. The claim further recites the steps taken to produce the mapping partner strain. To avoid any clarity issue, the claim is amended slightly to accentuate this point. Claim 7 remains a method for identifying a segregating single point mutation at a genetic locus that modifies an index phenotype in a non-human index inbred strain, as claimed in underlying Claim 1.

Claim 8 is said to be unclear and confusing in the recitation of "a wild-type inbred mouse." The Examiner imposes a limited meaning of the term "wild-type" in imposing the rejection. Applicants state for the record that the term is used in the claim and in the specification in a manner familiar to the art, namely that the so-called wild-type animal is a standard inbred strain that does not carry the random point mutations of the founder inbred strain. As before, applicants maintain that no claim amendment is required to clarify this to the skilled artisan.

Claim 26 is said to be incomplete because the final method step does not result in identification of a segregating mutation. As applicants read the claim, however, the identification in the N2 backcross progeny of at least one animal having a modified tumor multiplicity is indeed the identification of a segregating mutation. The claim specifies in its final clause that the modified tumor multiplicity is characteristic of the segregating mutation. The claim is amended slightly to incorporate the Examiner's suggestion that the segregating mutation is identified on that basis.

Claims 27 and 40 are said to be unclear for lack of antecedent basis. The issues noted by the Examiner are resolved in the amended claims such that antecedent basis exists for each element.

Claim 28 is said to be unclear and confusing for a lack of antecedent basis for "the

genetic background" and a lack of clarity as to what the genetic background should be. Amended Claim 28 addresses the issue raised by the Examiner.

Request for Confirmation

On pages 7 and 8 of the Office Action, the Examiner appears to withdraw a rejection under §102(a), where the Examiner states "Claims 1, 3-25 rejected under 35 U.S.C. 102(a) as being anticipated by Bilger et al. is withdrawn." However, after reiterating applicants' arguments, the Examiner concludes the section by stating "applicants' amendment has been fully considered, but found not persuasive."

There being no rejection affirmatively stated, applicants conclude that no rejection was maintained. Confirmation is respectfully requested.

Petition to Correct Inventorship

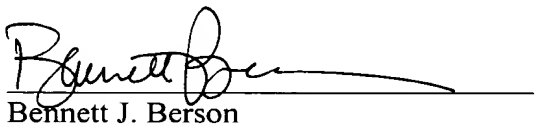
With its CPA application, filed April 8, 2002, applicants filed a Petition to Correct Inventorship. An update on the status of the petition is respectfully requested.

Having responded to each ground of rejection under 35 U.S.C. §112, second paragraph, applicants believe that the claims are in condition for allowance. Reconsideration is respectfully requested.

A petition for an extension of time for 2 months accompanies this response so the response will be deemed to have been timely filed. No additional extension of time is believed due, however should an extension be due, please consider this to be a request for the appropriate extension and a request to charge the fee due to Deposit Account No. 17-0055.

Likewise, no other fee is believed due, but should such a fee be due, please consider this to be a request to charge the fee to the same deposit account.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

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Date: November 19, 2002

Serial No.: 09/114,973

Group Art Unit: 1632

Filed: 07/14/98

Examiner: J. Woitach

Title: METHOD FOR IDENTIFYING MUTANTS AND MOLECULES

Docket No.: 960296.95491

In the Claims:

Please amend Claims 1, 7, 23, 25-28, 30, 36 and 40 as follows:

1. (Amended Three Times) A method for identifying a segregating single point mutation at a genetic locus that modifies an index phenotype in a non-human index inbred strain, the segregating mutation causing an outlying phenotype relative to the index phenotype, the method comprising the steps of:

outcrossing at least one male animal of a non-human founder inbred strain to at least one female animal of a non-human index inbred strain to obtain F1 progeny, the founder inbred strain carrying random point mutations relative to a wild-type animal of the founder inbred strain, the index inbred strain carrying a congenic dominant allele at a locus known to confer the index phenotype and being genetically distinguishable from the founder inbred strain, [wherein at least one of the F1 progeny that carry the dominant allele also carry at least one random mutation]

identifying one or more F_1 individuals displaying an outlying phenotype relative to the index phenotype displayed by the index inbred strain, thereby indicating that at least one F_1 individual possesses an index phenotype-modifying mutation;

backcrossing gametes from male F1 progeny to at least one female of the index inbred strain, with or without the index allele, to obtain N2 backcross progeny, wherein at least one of the N2 backcross progeny that carry the dominant allele also exhibit the outlying phenotype; and

verifying that the outlying phenotype is caused by a segregating single point mutation.

7. (Amended Two Times) A method as claimed in Claim 6 further comprising the step of mapping the segregating mutation using a mapping partner strain, the mapping partner strain being produced by the steps of:

treating an animal of [an index] the founder strain with a mutagenic agent to induce

point mutations in the treated animal;

crossing the treated animal to an animal of the [index] <u>founder</u> strain to produce [F1] <u>F_1</u> progeny; and

sib-mating [F1] <u>F_1</u> and subsequent generation progeny until detrimental and lethal mutations are eliminated.

23. (Amended) A non-human animal comprising a segregating mutation that modifies an index phenotype, the animal being prepared according to a method comprising the steps of:

outcrossing a founder [isogenic] inbred strain with the index inbred strain to obtain Gen1F_1 progeny, the founder [isogenic] strain being heterozygous only for random point mutations relative to a wild-type animal of the founder inbred strain, the index inbred strain carrying a dominant allele at a locus known to confer the index phenotype, where at least some of the Gen1F_1 progeny carry both the dominant allele and at least one random mutation;

crossing a founder animal of the founder [isogenic] inbred strain to an animal of the founder strain that lacks the mutations to obtain [inbred] Gen2 offspring, where the founder animal has at least one outcrossed F_1 progeny that displays the outlying phenotype relative to the index phenotype;

outcrossing Gen_2 offspring to the index strain to obtain Gen2F_1 backcross progeny, half of which, on average, carry the dominant allele that confers the index phenotype; and

verifying that a subset of the Gen2F_1 progeny shows the outlying phenotype; and

selecting an animal that shows the outlying phenotype.

25. (Amended) A method for identifying a segregating mutation at a genetic locus that modifies an index phenotype in a non-human index inbred strain, the segregating mutation causing an outlying phenotype relative to the index phenotype, the method comprising the steps of:

outcrossing a non-human founder [isogenic] inbred strain with the non-human index inbred strain to obtain Gen1F_1 progeny, the founder [isogenic] strain being heterozygous only for random point mutations relative to a wild-type animal of the founder inbred strain, the index inbred strain carrying a dominant allele at a locus known to confer the index phenotype, where at least some of the Gen1F_1 progeny carry both the dominant allele and at least one random mutation;

crossing a founder animal of the founder [isogenic] inbred strain to an animal of the founder strain that lacks the mutations to obtain [inbred] Gen2 offspring, where the founder animal has at least one outcrossed F_1 progeny that displays the outlying phenotype relative to the index phenotype;

outcrossing Gen2 offspring to the index strain to obtain Gen2F_1 backcross progeny, half of which, on average, carry the dominant allele that confers the index phenotype; and

verifying that a subset of the Gen2F_1 progeny shows the outlying phenotype.

26. (Amended) A method as claimed in Claim 6 wherein the method identifies a segregating mutation at a genetic locus that modifies tumor multiplicity in a C57BL/6 mouse congenic for the *Min* allele at the Apc locus, the method comprising the steps of:

outcrossing at least one male C57BL/6 mouse carrying random point mutations to a female C57BL/6 mouse congenic for the *Min* allele at the Apc locus to obtain F1 progeny[, wherein at least one of the F1 progeny carries both the *Min* allele and a random point mutation];

identifying one or more F_1 individuals displaying an outlying tumor multiplicity phenotype relative to the tumor multiplicity phenotype in a C57BL/6 mouse congenic for the *Min* allele at the Apc locus, thereby indicating that at least one F_1 individual possesses a segregating mutation that modifies tumor multiplicity;and

backcrossing gametes from male F1 progeny to at least one female C57BL/6 mouse congenic for the *Min* allele at the Apc locus to obtain N2 backcross progeny, wherein at least one of the N2 backcross progeny carries the *Min* allele and has a tumor multiplicity that is modified relative to tumor multiplicity in a C57BL/6 mouse congenic for the *Min* allele at the Apc locus, the modified tumor multiplicity being characteristic of the segregating mutation thereby identified.

27. (Amended Two Times) A method as claimed in Claim 26 wherein the modified tumor multiplicity is evaluated according to a method comprising the steps of:

repeatedly applying for random permutations of mice among N2 backcross subkindreds a likelihood ratio test of the null hypothesis that no multiplicity modifier is segregating to obtain a p-value, wherein a p-value of less than 0.05 indicates a potential carrier of the segregating mutation;

when the p-value is less than 0.05, calculating, for each potential carrier that has offspring with information about tumor multiplicity, a LOD score for presence of the

segregating mutation, wherein the LOD score is $\log_{10}$ of a ratio of [the] a first probability of offspring phenotype data if the potential carrier mouse carries a multiplicity modifier to [the] a second probability of offspring phenotype data if the potential carrier mouse does not carry a multiplicity modifier, and wherein the [denominator] second probabilities are calculated from an estimated background distribution and the [numerator] first probabilities are calculated from a mixture of the estimated background distribution and an estimated modified distribution, where the estimated distributions are obtained by [the method of] a maximum likelihood method; and

[mapping] ranking the LOD scores of [the] potential carriers, whereby animals having the highest LOD scores are likely carriers of the segregating mutation.

28. (Amended Two Times) A method as claimed in claim 26, further comprising the step of mapping the segregating mutation in the N2 backcross progeny using a mapping partner strain having a C57BL/6 genetic background.

30. (Amended) A method for identifying a segregating single point mutation at a genetic locus that modifies an index phenotype in a mouse index inbred strain, the segregating mutation causing an outlying phenotype relative to the index phenotype, the method comprising the steps of:

outcrossing at least one male animal of a mouse founder inbred strain to at least one female animal of a mouse index inbred strain to obtain F1 progeny, the founder inbred strain carrying random point mutations relative to a wild-type animal of the founder inbred strain, the index inbred strain carrying a congenic dominant allele at a locus known to confer the index phenotype and being genetically distinguishable from the founder inbred strain, [wherein at least one of the F1 progeny that carry the dominant allele also carry at least one random mutation]

identifying one or more F_1 individuals displaying an outlying phenotype relative to the index phenotype displayed by the index inbred strain, thereby indicating that at least one F_1 individual possesses an index phenotype-modifying mutation;

backcrossing gametes from male F1 progeny to at least one female of the index inbred strain, with or without the index allele, to obtain N2 backcross progeny, wherein at least one of the N2 backcross progeny that carry the dominant allele also exhibit the outlying phenotype; and

verifying that the outlying phenotype is caused by a segregating single point mutation.

36. (Amended) A method as claimed in Claim 35 further comprising the step of mapping the segregating mutation using a mapping partner strain produced by the steps of:

treating an animal of [an index] the founder strain with a mutagenic agent to induce point mutations in the treated animal;

crossing the treated animal to an animal of the [index] founder strain to produce [F1] F_1 progeny; and

sib-mating [F1] F_1 and subsequent generation progeny until detrimental and lethal mutations are eliminated.

40. (Amended) A method as claimed in Claim 39 wherein the modified tumor multiplicity is evaluated according to a method comprising the steps of:

repeatedly applying for random permutations of mice among N2 backcross subkindreds a likelihood ratio test of the null hypothesis that no multiplicity modifier is segregating to obtain a p-value, wherein a p-value of less than 0.05 indicates a potential carrier of the segregating mutation;

when the p-value is less than 0.05, calculating, for each potential carrier that has offspring with information about tumor multiplicity, a LOD score for presence of the segregating mutation, wherein the LOD score is $\log_{10}$ of a ratio of [the] a first probability of offspring phenotype data if the potential carrier mouse carries a multiplicity modifier to [the] a second probability of offspring phenotype data if the potential carrier mouse does not carry a multiplicity modifier, and wherein the [denominator] second probabilities are calculated from an estimated background distribution and the [numerator] first probabilities are calculated from a mixture of the estimated background distribution and an estimated modified distribution, where the estimated distributions are obtained by [the method of] a maximum likelihood method; and

ranking the LOD scores of the potential carriers, whereby animals having the highest LOD scores are likely carriers of the segregating mutation.